Remarks

Claims 1, 2, and 21 were pending; claim 1 is amended herein and new claims 22-26 are added. As a result, claims 1, 2, and 21-26 are pending. The new and amended claims are supported throughout the originally filed specification and claims. Amended claim 1 is supported, e.g., by originally filed claims 1, 4, 14, and 15, by SEQ ID NO:5, and by paragraph [0046] of the specification, and by SEQ ID NOS:1 and 4. Claim 22 is supported by paragraphs [0009], [0011], [0041], and [0046]. Paragraph [0009] discloses that the extracellular amino terminal domain is encoded by exons 1-9, as set out in SEQ ID NO:1. It discloses that exon 4 is nucleotides 34575 to 38024 of SEQ ID NO:1. Paragraphs [0011] and [0041] disclose that the amino terminal extension comprises (is encoded by) four genomic exons [exons 1-4 described in paragraph 0009]. A comparison of the sequence of exon 4 (nucleotides 34575-38024 of SEQ ID NO:1) and the cDNA of SEQ ID NO:4 reveals that exon 4 ends at nucleotide 31,485 of SEQ ID NO:4. A comparison of the sequences of exons 1-4 of SEQ ID NO:1, the cDNA sequence of SEQ ID NO:4, and the protein sequence of SEQ ID NO:5 reveals that exons 1-4 encode residues 1-10,427 of SEQ ID NO:5. New claims 22-26 are additionally supported by paragraph [0046] and originally filed claims 14 and 15. Paragraph [0046] discloses expressing portions of the cDNA to make CA125 polypeptides, and using these CA125 protein portions, such as the amino terminal sequence, to make monoclonal antibodies. Originally filed claims 14 and 15 disclose fragments of SEQ ID NO:5 and antibodies that bind to SEQ ID NO:5 and fragments thereof.

Double Patenting

Claim 2 is provisionally rejected under 35 U.S.C. § 101 as claiming the same invention as that of claim 25 of copending application no. 10/475,117. This rejection is respectfully traversed.

Claim 2 recites an isolated nucleic acid molecule comprising the sequence of SEQ ID NO: 4, wherein the isolated nucleic acid molecule is an expression vector and is adapted to express in a cell CA125 (SEQ ID NO:5) or a fragment thereof. Claim 25 of copending application no. 10/475,117 does not recite that the isolated nucleic acid is an expression vector and is adapted to express in a cell CA125 (SEQ ID NO:5) or a

fragment thereof. Accordingly, the two claims do not claim the same subject matter, and the double-patenting rejection under 35 U.S.C. § 101 is not appropriate (M.P.E.P. § 804A).

In view of the amendments and remarks, Applicants respectfully request withdrawal of the provisional rejection of claim 2 for double patenting under 35 U.S.C. § 101 over copending application no. 10/475,117.

The Rejections of the Claims Under 35 U.S.C. § 112

Claims 1 and 21 were rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. This rejection is respectfully traversed.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, "Written Description" Requirement, Fed. Register 66:1099-1111 (Written Description Guidelines) states, "While there is no *in haec verba* requirement, newly added claim limitations must be supported in the specification through express, implicit, or inherent disclosure" (Written Description Guidelines, at 1105).

The Examiner has the initial burden of presenting evidence or reasoning to explain why persons skilled in the art would not recognize in the original disclosure a description of the invention defined by the claims. (Written Description Guidelines, at 1107, citing *In re Wertheim*, 541 F.2d 257, 262, 191 USPQ 90, 96 (Ct. Customs and Patent Appeals 1976).

The Board of Patent Appeals and Interferences in *Ex parte Parks*, 30 U.S.P.Q.2d 1234 (Bd. Pat. App. & Int. 1994) stated:

> Adequate description under the first paragraph of 35 U.S.C. 112 does not require *literal* support for the claimed invention. . . . Rather, it is sufficient if the originally filed disclosure would have conveyed to one having ordinary skill in the art that an appellant had possession of the concept of what is claimed. (Emphasis added.)

Amended claim 1 recites "an isolated nucleic acid molecule encoding CA125 (SEQ ID NO:5) or a fragment thereof; wherein the isolated nucleic acid molecule is an expression vector and is adapted to express in a cell CA125 (SEQ ID NO:5) or a fragment thereof." This is abundantly supported in the specification. It is supported, e.g., by originally filed claims 1, 4, 14, and 15, by SEQ ID NO:5, and by paragraph [0046] of

the specification, and by SEQ ID NOS:1 and 4. Paragraph [0046] discloses expressing portions of the cDNA encoding CA125 to make CA125 polypeptides, and using these portions of the CA125 protein to make monoclonal antibodies. One of skill in the art would therefore have no doubt that Applicants were in possession of invention of claim 1.

Regarding claim 21, originally filed claims 5 and 7 explicitly disclose SEQ ID NO:1 and fragments thereof.

Regarding the present claims 22 and 24, the Examiner stated in the Office Action "there is nothing in the specification to suggest the limitation of a polypeptide comprising residues 1-10,427 of SEQ ID NO:5 or a fragment of residues 10,427 of SEQ ID NO:5 recognized by an antibody that selectively binds to SEQ ID NO:5." By this he apparently means that the exact words of claim 1 in full are not recited in the application as filed. But the Written Description Guidelines explicitly state that compliance with the first paragraph of 35 U.S.C. 112 does not require literal support for the claimed invention.

The Examiner has not met his burden to establish a *prima facie* case of unpatentability under the written description requirement because the Examiner has made no attempt to analyze what one of skill in the art would understand from the application as filed, and why such a person would not recognize the concept of what is claimed in claims 22 and 24.

Paragraph [0009] discloses that the extracellular amino terminal domain is encoded by exons 1-9, as set out in SEQ ID NO:1. It discloses that exon 4 is nucleotides 34575 to 38024 of SEQ ID NO:1. Paragraphs [0011] and [0041] disclose that the amino terminal extension comprises (is encoded by) four genomic exons [exons 1-4 described in paragraph 0009]. A comparison of the sequence of exon 4 (nucleotides 34575-38024 of SEQ ID NO:1) and the cDNA of SEQ ID NO:4 reveals that exon 4 ends at nucleotide 31,485 of SEQ ID NO:4. A comparison of the sequences of exons 1-4 of SEQ ID NO:1, the cDNA sequence of SEQ ID NO:4, and the protein sequence of SEQ ID NO:5 reveals that exons 1-4 encode residues 1-10,427 of SEQ ID NO:5. There is thus literal and inherent support for a fragment of CA125 comprising residues 1-10,427 of SEQ ID NO:5 and an isolated nucleic acid molecule encoding this fragment.

Originally filed claim 14 explicitly discloses a fragment of SEQ ID NO:5. Claim 15 explicitly discloses an antibody that binds to a fragment of SEQ ID NO:5 and to CA125 SEQ ID NO:5. Paragraph [0046] explicitly discloses expressing portions of CA125 from a vector and using them to make antibodies. Paragraph [0046] also explicitly discloses expressing and making monoclonal antibodies to portions of CA125, including "the amino terminal sequence."

The specification as filed thus explicitly discloses SEQ ID NO:5 as a full-length sequence of CA125. It explicitly discloses an amino terminal extension fragment of CA125 comprising residues 1-10,427 of SEQ ID NO:5. It explicitly discloses fragments of SEQ ID NO:5 recognized by antibodies that selectively bind to CA125 SEQ ID NO:5. It explicitly discloses isolated nucleic acids encoding SEQ ID NO:5 and fragments thereof. It explicitly discloses isolated SEQ ID NO:1 and fragments thereof. It explicitly discloses expressing portions of SEQ ID NO:5 from an expression vector and using the expressed portions of CA125 SEQ ID NO:5 to make antibodies. Based on that disclosure, it is clear that one of ordinary skill in the art would have no doubt that Applicants were in possession of the concept of the inventions of the pending claims.

The Examiner next stated in section 8 of the Office Action that "If applicant were able to overcome the rejections set forth above, claims 1 and 21 would still be rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for an isolated nucleic acid molecule that encodes a polypeptide consisting of residues 1-10,427 of SEQ ID NO:5 recognized by an antibody that selectively binds to SEQ ID NO:5, . . . does not reasonably provide enablement" for an isolated nucleic acid molecule as claimed in claim 1. The Examiner has orally told Applicant's representative that this is an enablement rejection and is not dependent upon the written description rejection traversed above. This rejection is respectfully traversed.

The Examiner characterized the claims as meaning that an antibody that selectively binds SEQ ID NO:5 can also recognize any polypeptide comprising a fragment of residues 1-10,427 of SEQ ID NO:5.

That is not what the previous claim 1 recited, and it is not what the present claims recite. Claim 1 recites "an isolated nucleic acid molecule encoding CA125 (SEQ ID

NO:5) or a fragment thereof; wherein the isolated nucleic acid molecule is an expression vector and is adapted to express in a cell CA125 (SEQ ID NO:5) or a fragment thereof." Antibodies are nowhere recited.

Claims 23 and 24 recite an isolated nucleic acid molecule of claim 1 wherein the isolated nucleic acid molecule encodes and is adapted to express in a cell a fragment of SEQ ID NO:5 wherein the expressed fragment can be used to make monoclonal antibodies. It is stated in paragraph [0046] of the specification that fragments of CA125 can be expressed and used to make antibodies, and the Examiner has presented no evidence or reasoning to doubt that statement.

Claims 25 and 26 recite that the expressed fragment can be used to make monoclonal antibodies that specifically recognize CA125 (SEQ ID NO:5). The Examiner argued against enablement of the previous claims by stating that not every antibody that recognizes a full-length protein also recognizes a particular fragment of that protein. Obviously that is true, but it is irrelevant. The claims do not recite that.

Antibodies recognize short peptide epitopes of complete proteins, and therefore an antibody that recognizes a short sequence within a full-length protein will not recognize other peptide fragments of the protein not containing that short sequence, as the Examiner implies. But the present claims do not recite that every antibody that recognizes CA125 also recognizes a particular fragment of CA125. Instead, claims 25 and 26 recite an isolated nucleic acid molecule of claim 1 wherein the isolated nucleic acid molecule encodes and is adapted to express in a cell a fragment of SEQ ID NO:5 wherein the expressed fragment can be used to make monoclonal antibodies that specifically recognize CA125 (SEQ ID NO:5).

Any antibody that recognizes a peptide fragment of a protein is likely to recognize the full-length protein. And it can be easily tested whether an antibody that recognizes a particular fragment of CA125 also recognizes full-length CA125 by testing the antibody for recognition of full-length CA125.

This is supported by Abaza (*J. Protein Chem.* 11:433-444, 1992), although the Examiner cited Abaza to argue against enablement. Abaza instead supports the enablement of the claimed invention. Abaza states in the abstract "Amino acid substitutions outside protein antigenic sites are very frequently assumed to exert no effect

on binding to antiprotein antibodies." This implies that those of skill in the art assume that an antibody that recognizes a peptide within a protein will also recognize the full-length protein. Abaza's data supports this assumption. Abraza reports testing three monoclonal antibodies that recognize peptide 94-100 of sperm whale myoglobin (page 435, second column) for recognition of myoglobins from several species. Abraza reports that all three monoclonal antibodies specifically recognized every myoglobin tested where the myoglobin had no alterations in peptide 94-100, regardless of alterations elsewhere in the protein (page 435-436 and Figures 2 and 3). The affinity of the monoclonal antibodies varied between the different proteins tested, but all three monoclonal antibodies specifically recognized every variant myoglobin having the peptide sequence.

Thus, if the question is whether a monoclonal antibody recognizing a particular peptide will recognize a protein containing that peptide, the answer according to Abraza was yes in 18 of 18 permutations tested (3 monoclonal antibodies x 6 protein variants). This suggests a very high likelihood of success that an antibody that recognizes a fragment of CA125 will also recognize the full-length CA125.

The Examiner states: "Although Applicants might argue that one of ordinary skill could screen for species that would function as claimed, in particular, screening assays do not enable the claimed invention because the court found in (*Rochester v. Searle*, 358 F.3d 916, Fed Cir., 2004) that screening assays are not sufficient to enable an invention because they are merely a wish or plan for obtaining the claimed chemical invention. *Rochester v. Searle* does not address the enablement requirement at all. The court stated, "In view of our affirmance of the district court's decision on the written description ground, we consider the enablement issue to be moot and will not discuss it further." Thus, the Federal Circuit in *Rochester v. Searle* certainly did not hold that screening assays may not enable an invention, or anything of the sort. It did not address the enablement requirement at all.

The standard for determining compliance with the enablement requirement is whether one of skill in the art can make and use the invention without undue experimentation. M.P.E.P. 2164.01, citing *In re Wands*, 858 F.2d at 737 (Fed. Cir. 1988). The key word is "undue" not "experimentation." *In re Angstadt*, 537 F.2d 498, 190

U.S.P.Q. 214, 219 (C.C.P.A. 1976). The fact that experimentation may be complex does not necessarily make it undue if the art typically engages in such experimentation. M.P.E.P. 2164.01.

The Federal Circuit has explicitly recognized that the requirement for extensive screening programs to locate and identify bioactive molecules does not constitute undue experimentation. In *In re Wands*, 8 U.S.P.Q.2d 1400, 1406-07 (Fed. Cir. 1988). The court stated:

> The nature of monoclonal antibody technology is that it involves screening hybridomas to determine which one secretes antibody with desired characteristics. Practitioners of this art are prepared to screen negative hybridomas in order to find one that makes the desired antibody.

To practice the presently claimed invention requires no screening at all. The precise sequences of SEQ ID NO:5 and of a cDNA encoding it, SEQ ID NO:4 are given. The application is therefore enabled.

If one wanted to determine whether a fragment of SEQ ID NO:5 encoded by a nucleic acid of claims 25 and 26 were recognized by an antibody that recognizes CA125 it would be a simple screening experiment to raise antibodies against the fragment of SEQ ID NO:5 and then determine whether the antibodies specifically recognized CA125. According to the data presented in Abaza, one would expect that close to 100% of antibodies that recognize a peptide fragment of SEQ ID NO:5 would recognize the full-length CA125. This success rate is much higher than the success rate of most screening programs in the biological sciences, such as the screening program in *In re Wands*, which was determined by the Federal Circuit not to constitute undue experimentation.

The Examiner makes a further argument against the enablement of the claimed invention on page 6 of the Office Action, where he states that Bowie et al. teach that "the position within a protein's sequence where amino acid alterations can be made with a reasonable expectation of maintaining function are limited." This has nothing to do with the claimed invention since the claims recite "an isolated nucleic acid molecule encoding CA125 (SEQ ID NO:5) or a fragment thereof." That does not allow for any amino acid alterations.

It is respectfully submitted that the claims and specification clearly comply with the enablement requirement, and withdrawal of the rejection of claims 1 and 21 as failing to comply with the enablement requirement of 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claims 1 and 21 were rejected again in section 9 of the Office Action under 35 U.S.C. § 112, first paragraph, as lacking an adequate written description in the specification. This rejection is respectfully traversed.

Claim 1 recites "an isolated nucleic acid molecule encoding CA125 (SEQ ID NO:5) or a fragment thereof."

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, ¶1, "Written Description" Requirement, Fed. Register 66:1099-1111 (Written Description Guidelines) states: "The complete structure of a species of a species or embodiment typically satisfies the requirement that the description be set forth "in such full, clear, concise, and exact terms" to show possession of the claimed invention. If a complete structure is disclosed, the written description requirement is satisfied for that species or embodiment, and a rejection under 35 U.S.C. 112, ¶1, for lack of written description must not be made."

Here, the complete structure of "An isolated nucleic acid molecule encoding CA125 (SEQ ID NO:5) or a fragment thereof" is disclosed in the specification and recited in claim 1. The complete structures of genomic nucleic acid sequences encoding SEQ ID NO:5 and fragments thereof are disclosed in the specification in SEQ ID NOS:1-3. The complete structure of a cDNA encoding SEQ ID NO:5 is disclosed as SEQ ID NO:4. The complete structure of any other nucleic acid encoding SEQ ID NO:5 or a a fragment thereof is disclosed by the disclosure of SEQ ID NO:5 in the specification and by the knowledge of the genetic code. The complete and exact structure of every possible species within the genus claimed by claim 1 is disclosed in the specification. Thus, a rejection under the written description requirement "must not be made" under the guidelines.

The Examiner cited *Univ. of California v. Eli Lilly and Co.*, 119 F.3d 1559, 43 U.S.PQ2d 1398 (Fed. Cir. 1997), to argue the claims do not satisfy the written description

requirement. *Lilly* instead shows that the present specification does satisfy the written description requirement for the claimed invention. *Lilly* concerned a University of California patent disclosing the isolation and sequencing of rat insulin cDNA, and the issue of whether this disclosure provided adequate support for claims generically reciting vertebrate insulin cDNA and mammalian insulin cDNA. (*Lilly*, 43 USPQ2d at 1404-1405.) The patentee disclosed only a process for obtaining human insulin-encoding cDNA or other mammalian insulin cDNAs other than rat. (*Lilly*, 43 USPQ2d at 1405.) The patentee had not disclosed the structure of human insulin cDNA but only a plan for obtaining it. In contrast, the present claims 1, 2, and 21 recite the precise structure of CA125 (SEQ ID NO:5). This also, with knowledge of the genetic code, inherently discloses the structure of every nucleic acid encoding SEQ ID NO:5 or a fragment thereof.

Furthermore, although in this case every species within the scope of claim 1 is described, the court in Lilly, stated: "[E]very species in a genus need not be described in order that a genus meet the written description requirement." *Lilly*, 43 USPQ2d at 1405.

On pages 11 and 12 the Examiner appears to argue that no species falling within the claims is disclosed. This is plainly not true. Applicants disclosed the complete sequence of two nucleic acids encoding SEQ ID NO:5 – genomic sequence SEQ ID NO:1 and cDNA SEQ ID NO:4. The CA125 protein (SEQ ID NO:5) is known to be recognized by antibodies, as recited in claims 25 and 26. The specification discloses expressing a fragment of SEQ ID NO:5 from an expression vector, and that this fragment is recognized by antibodies that recognize CA125 (Figures 4 and 5 of parent application serial no. 09/965,738, incorporated by reference in paragraph 1 of the present application).

The present specification clearly satisfies the written description requirement of the claimed invention. The applicants provided the complete and precise structure of nucleic acids encoding SEQ ID NO:5 and fragments thereof. This is specifically held to satisfy the written description requirement in *Lilly*, and is stated to do so under the Written Description Guidelines. In addition, Applicants provide an expression vector expressing a fragment of SEQ ID NO:5 that is recognized by an antibody that recognizes

CA125. Therefore, Applicant respectfully requests withdrawal of the rejection of claims 1 and 21 under 35 U.S.C. § 112, first paragraph.

The Rejection of the Claims Under 35 U.S.C. § 102

Claims 1 and 21 were rejected under 35 U.S.C. 102(b) as being anticipated by DOE Joint Genome Institute, Homo sapiens chromosome 19 clone CTD-2596015, Accession No. AC016584, version AC016584.2, GI 6758722, January 26, 2000. This rejection is respectfully traversed.

A reference anticipates a claim under 35 U.S.C. § 102, "only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." M.P.E.P. §2131; *Verdegaal Bros. v. Union Oil Co. of California* 814 F.2d 628,631, 2 U.S.P.Q.2d 1051, 1053 (Fed. Cir. 1987).

Claim 1 recites "an isolated nucleic acid molecule encoding CA125 (SEQ ID NO:5) or a fragment thereof; wherein the isolated nucleic acid molecule is an expression vector and is adapted to express in a cell CA125 (SEQ ID NO:5) or a fragment thereof."

AC016584 discloses the sequence of a portion of human Chromosome 19. It does not disclose that the sequence is in an expression vector adapted to express in a cell CA125 (SEQ ID NO:5) or a fragment thereof. Therefore it does not disclose all the elements of any of the present claims and does not anticipate any of the present claims.

In view of the amendments and remarks, withdrawal of the rejection of claims 1 and 21 under 35 U.S.C. 102(b) as anticipated by Accession No. AC016584 is respectfully requested.

Conclusion

The Examiner is invited to telephone Applicant's attorney (651-207-8270) to facilitate prosecution of this application. Applicants believe the claims are in condition for allowance, and notification to that effect is respectfully requested.

Respectfully submitted,

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CERTIFICATE UNDER 37 CFR 1.8: The undersigned hereby certifies that this correspondence is being deposited with the United States Postal Service with sufficient first class postage, in an envelope addressed to: Mail Stop RCE, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450, on this day April 6, 2007.

Hugh McTavish